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10/804,785	03/19/2004	Frits Goedegebuur	GC793-3	7768

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VICTORIA L. BOYD  
GENENCOR INTERNATIONAL, INC.  
925 PAGE MILL ROAD  
PALO ALTO, CA 94304-1013

EXAMINER
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RAGHU, GANAPATHIRAM

ART UNIT	PAPER NUMBER
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1652

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10/17/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/804,785	Applicant(s) GOEDEGEBUUR ET AL.	
	Examiner Ganapathirama Raghu	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 1-5 and 8-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 6 and 7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

***Application Status***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/29/07 has been entered.

In response to the Final Office Action mailed on 03/09/2007, applicants' filed an RCE received on 09/06/07 is acknowledged. Said RCE amended claims 6 and 7. Claims 1-25 are pending, claims 1-5 and 8-25 are withdrawn as they are drawn to non-elected inventions and thus claims 6 and 7 are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

***Maintained-Claim Rejections: 35 USC § 112  
Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant *H. jecorina* CBH1, wherein in said variant consists of SEQ ID NO: 1 with the amino acid residue T66 has been substituted or deleted, the specification does not reasonably provide enablement for any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any substitution corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope

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with the claim (mere recitation of sequences from prior art in the specification does not overcome the deficiency in the scope of the claims).

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6-7 are so broad as to encompass any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1. Thus the claimed cellulases have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants of *H. jecorina* CBH 1 cellulase protein as broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to a variant *H. jecorina* CBH1, wherein in said variant

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consists of SEQ ID NO: 1 with the amino acid residue T66 has been substituted or deleted, but provides no guidance with regard to making and using variants of *H. jecorina* CBH1 cellulase i. e., any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1. In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions,

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including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1, because the specification does not establish: **(A)** the desired CBH 1 activity of all polypeptides including variants of *H. jecorina* CBH1; **(B)** regions of the protein/polynucleotide structure which may be modified without affecting the activity of encoded polypeptide; **(C)** the general tolerance of the polypeptide and the polynucleotide encoding to modification and extent of such tolerance; **(D)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(E)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants' have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of encompasses any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection of claims 6 and 7 under 35 U.S.C. 112 for enablement be withdrawn, applicants', provide the following argument.

(A) Claims as amended recites variant *H. jecorina* CBH 1 cellulase.

(B) Applicants' have identified possible sites involved in the stability of the CBH1 enzyme in three different ways... and the specification teaches a variant CBH1 polypeptide comprising a substitution or deletion at a position corresponding to one or more residues.

The argument is not found to be persuasive for the following reasons.

(A) & (B) Reply: Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The claims as written when given the broadest interpretation reads on any CBH1 cellulase, wherein said cellulase comprises a substitution or deletion at the position corresponding to T66 of SEQ ID NO:1 as "comprises" is considered to be "open language" and therefore said variant *H. jecorina* CBH 1 cellulase is not limited to substitution or deletion to amino acid residue T66 alone. Furthermore, said variant comprises any substitution (any other 19 amino acids), corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186 (E), S195 (A/F), E239S, G242 (H/Y/N/S/T/D/A) and P412 (T/S/A).

There is no guidance beyond the three ways to identify possible amino acid residues involved in thermostability of *H. jecorina* CBH 1 cellulase specific variants with specific amino acid residue substitution i. e., deletion of T66 amino acid residue and said deletion variant further comprising a substitution at a position corresponding to residue Q186 (E), S195 (A/F), E239S, G242 (H/Y/N/S/T/D/A) and P412 (T/S/A). The breadth of the modification (as claimed in claims

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6 and 7) encompasses any variant *H. jecorina* CBH 1 cellulase not limited to substitution or deletion to amino acid residue T66 alone or any amino acid residue substitution at position T66 of *H. jecorina* CBH 1 cellulase and said variant further comprising any permutation or combination of substitutions such as Q186 (E), S195 (A/F), E239S, G242 (H/Y/N/S/T/D/A) and P412 (T/S/A) and there is no limitation either to the substitution at T66 or other permutations and combinations as claimed in claim 7. Although applicants have shown how to make the variants by way of three examples, applicants have not established how to use other claimed variants as encompassed by the claims, i.e., the structure-function correlation is not established in the specification for all the variants and mutants i.e., any variant *H. jecorina* CBH 1 cellulase not limited to substitution or deletion to amino acid residue T66 alone or substitution of any amino acid residue at T66 and said variant having any permutation and combination of changes at Q186 (E), S195 (A/F), E239S, G242 (H/Y/N/S/T/D/A) and P412 (T/S/A) and said variant having the property of increased thermostability. Furthermore, it is also well known in the art, for example substitution with any amino acid residue with bulky aromatic group or side chain or helix breaking amino acid residue like proline will alter the configuration of the molecule or the thermostability property. Hence, while methods to produce variants of a known sequence, such as insertion mutagenesis, site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants useful as claimed any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1, requires that one of ordinary skill in the art know or be provided with



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guidance for the selection of which of the infinite number of variants have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, this would clearly constitute **undue** experimentation.

*Written description*

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As outlined supra, applicant has apparently not made and analyzed all of the mutant CBHI enzymes of the instant claims and therefore it is maintained that at the time of filed one of skill in the art would not conclude that applicant had possession of the claimed invention.

Claims 6-7 (as interpreted), are directed to (1) a genus of variant CBH 1 polypeptides from any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1. Furthermore, the claim language as written allows substitution at all positions of said mature *H. jecorina* CBH1 protein of SEQ ID NO: 1. While the specification discloses the structure of a variant *H. jecorina* CBH1, wherein in said variant the amino acid residue T66 has been deleted from the wild-type sequence of SEQ ID NO: 1, the specification is silent in regard to (1) the structures of all the polypeptides encompassed by the claims, (2) the critical structural elements of any variant CBH 1 polypeptide

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from any source wherein said variant comprises any source, wherein said variant comprises any substitution or deletion, corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A), which have any % sequence identity to the polypeptide of SEQ ID NO:1.

The genus of polypeptides required in the claimed invention is an extremely large structurally variable genus. While the argument can be made that the recited genus of polypeptides is adequately described by the disclosure of the structure of the polypeptide of SEQ ID NO: 1, since one could use structural homology to isolate those polypeptides recited in the claims, as taught by the art, even highly structurally homologous polypeptides do not necessarily share the same function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a  $\beta$ -ketoacyl synthase into a malonyl decarboxylase and completely eliminates  $\beta$ -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8): 2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, the claimed genera of polypeptides have the potentiality of encoding proteins of many different functions.

In addition, while a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by amino acid

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sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, the interpreted structural feature, i.e. “any variant *H. jecorina* CBH 1 cellulase, wherein said variant comprises any number of substitutions, including a substitution of position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and the claimed cellulase have no recited structural limitations except for the lack of threonine at position corresponding to position 66 of SEQ ID NO: 1”, does not constitute a substantial portion of the genus as the remainder of any polypeptide comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. Many structurally unrelated polypeptides are encompassed by these claims. The specification only discloses a single species of the recited genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

In response to the above rejection, applicants have traversed on the basis that: “specification teaches the variant CBH 1 polypeptides comprise a substitution or deletion at apposition corresponding to one or more residues including *inter alia*, sites presently claimed in claim (T66) and claim 7 (Q186, S195, E239, G242, P412)”.

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Applicants' arguments have been fully considered but are not deemed persuasive, because as suggested in the above rejection claim language as written is directed to extremely large functionally and structurally variable genus, as "comprising" is considered to be "open language".

***Maintained-Claim Rejections: 35 USC § 102***

Previous rejection of claim 6 under 35 U.S.C. 102(b) as being anticipated by either of (A), von der Osten, et al. (B), Schulein, et al. (C), Miettinen-Oinonen, et al. or (D) Lund. von der Osten (A), as shown by the sequence search (V), has T66 substituted with S in SEQ ID NO:1. Schulein, et al. (B), as shown by the sequence search (W), has T66 substituted with S and T66 deleted in SEQ ID NO: 11. Meittinen-Oinonen, et al. (C), as shown by the sequence search (X), has T66 substituted in SEQ ID NO: 33 and 35. Lund, et al. (D), as shown by the sequence search (U-I), has T66 substituted by S in SEQ ID NO: 1-3 is withdrawn in view of the amendment to claim 6 as the amended claim is directed to variant *H. jecorina* CBH1 cellulase.

Claims 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Radford, et al. (A). Radford, et al., as shown by the sequence searches (U), has T66 deleted in SEQ ID NO:3, T66 substituted with S and G242 substituted with S in SEQ ID NO:2 and T66 substituted with S and G242 substituted with S in SEQ ID NO:3.

In response to the above rejection, applicants have traversed on the basis that: "cited reference sequences have low homology to *H. jecorina* CBH 1 and does not teach each and every element of claims...".

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons, because as suggested in the above 112 first paragraph rejections, claim

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language as written is directed to extremely large functionally and structurally variable genus, as “comprising” is considered to be “open language”. Thus, the claims as written when given the broadest interpretation include any cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion at a position corresponding to T66 of *H. jecorina* CBH1 protein of SEQ ID NO: 1, since there is NO DEFINITION of a “variant *H. jecorina* CBH1 cellulase”. Any cellulase which differs from *H. jecorina* CBH 1 can be considered a variant CBH 1 cellulase, as applicants’ have not defined any limitations which must be present in such variant *H. jecorina* CBH 1 cellulase. Furthermore, the cited references have annotated their respective polypeptides as cellulases, therefore claims as written read on cited prior art references.

Applicants’ arguments have been fully considered but are not deemed persuasive,

#### ***Summary of Pending Issues***

The following is a summary of issues pending in the instant application.

- 1) Claims 6 and 7 are rejected under 35 U.S.C. first paragraph for enablement and written description.
- 2) Claim 6 under 35 U.S.C. 102(b) as being anticipated by either of (A), yon der Osten, et al. (B), Schulein, et al. (C), Miettinen-Oinonen, et al. or (D) Lund. yon der Osten (A).
- 3) Claims 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Radford, et al. (A).

#### ***Allowable Subject Matter/Conclusion***

None of the claims are allowable. Claims 6 and 7 are rejected for the reasons identified in the Summary section of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

#### *Final Comments*

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants'

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remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.  
Patent Examiner  
Art Unit 1652  
Oct. 05, 2007.

  
REBECCA S. DOOLY  
PATENT EXAMINER  
Art Unit 1652